UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/752,032	11/19/96	BOYCE	F 00786/206002

HM22/1229

ELDORA ELLISON FLOYD, ESQUIRE
STERNE, KESSLER, GOLDSTEIN, & FOX P.L.L.
1100 NEW YORK AVE, N.W.
SUITE 600
WASHINGTON, DC 20005-3934

EXAMINER	
BRUNOVSKIS,P	
ART UNIT	**PAPER NUMBER**
1632	19

DATE MAILED: 12/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/752,032	Applicant(s) Boyce
	Examiner P ter Brunovskis	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Oct 19, 1998*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Finality of the previous Office action is hereby withdrawn as are the previously indicated allowability of claim 1 in view of the new grounds for rejection presented below. Applicant's After Final Response, filed 10/19/00 has been entered. Claim 1 is pending in the instant application. Applicant's arguments filed 6/17/98 will be considered to the extent that they apply to the grounds of rejection set forth below against pending claim 1; arguments directed to any other subject matter is considered moot.

Information Disclosure Statement

DE 44 07 859 C1 (Reference BB) was only considered with respect to the English abstract provided in the Derwnet WP1 English language abstract for DE 44 07 859 C1 (Reference FN), since no further translation of the subject matter in Reference BB was supplied.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is broadly drawn to a method of expressing an exogenous gene in a mammal comprising introducing into the cell therein a baculoviral vector comprising an exogenous gene or comprising introducing into a mammal cells comprising a recombinant baculovirus carrying an exogenous gene. The only context in which the claimed method is presented in the specification is in the context of therapeutic delivery to treat liver diseases. The specification does not provide any evidence at the time the invention was made of Applicants having contemplated any non-therapeutic in vivo use, or any other therapeutic use for non-liver diseases, such as colon or breast cancer. Moreover, the specification provides no guidance or evidence teaching the use of the claimed baculoviral vectors to infect non-liver cells. The instant specification does not provide an enabling disclosure for the general method in vivo or ex vivo baculoviral-mediated gene delivery because the specification neither provides a well-established non-therapeutic utility for the claimed method, nor does it provide an enabling disclosure for therapeutic use for reasons of record previously applied to cancelled claims 21-26 and as further presented below.

Although the specification provides working examples demonstrating exogenous gene expression in hepatocyte cell culture systems, the evidence of record fails to disclose or provide any evidence of a well-established utility for in vivo delivery in animals that is non-therapeutic in nature. Moreover, the only context in which the claimed method is presented in the specification

is in the context of therapeutic delivery to treat liver diseases. Therefore, claim 1 is interpreted as being drawn to a method for therapeutic delivery of virus vectors for liver disease by *in vivo* or *ex vivo* gene transfer for which the specification does not provide an enabling disclosure. Claim 1 is not enabled because the specification does not provide sufficient guidance for one of skill in the art to use the claimed baculoviral vectors or cells comprising such for any therapeutic use outlined in the specification. Specifically, there is insufficient guidance concerning specific promoters, routes of delivery, dosage amounts (either vectors or cells comprising), frequencies of administration, expression levels, or any combination of these parameters for achieving a therapeutic benefit in mammals.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient delivery and expression of genes encoding the therapeutic protein sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. This is not to say that gene delivery and expression at a sub-therapeutic level was unpredictable at the time of filing. Blau et al stated that the main challenge in gene therapy is the achievement of efficient vector delivery and gene expression (Blau et al (1995), page 1204, col. 1-2 bridg. Sent. and page 1205, col. 1-2 bridg. Sent.). Crystal (1995) stated that human gene transfer still faces significant hurdles before it becomes an established therapeutic strategy (abstract) and that the human transfers had been plagued with inconsistent results (page 409, col. 1, parag. 2, lines 1-4). Miller et al (1995) that before gene therapy is an option for treating genetic diseases, there is a requirement to produce

vector systems that can deliver therapeutic genes to the appropriate target cells either in vivo or ex vivo accurately and efficiently (page 190, col. 1, parag. 1, lines 1-7).

Orkin et al. reviewed the infant state of the art of gene therapy at around the time the invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). The specification does not teach how one skilled in the art is to overcome any of the problems that have plagued gene therapy.

Verma et al (1997) states that gene delivery is the "Achilles heel" of gene therapy, and that the ability to deliver and expression genes efficiently to obtain sustained expression is needed for effective therapy (page 239, col. 3, parag. 1.). Ross et al (1996) state that the technical impediment to gene transfer (as a therapy) is the lack of vector systems, and that unless it is possible to deliver the gene to the appropriate blood or body cells and in sufficient quantities, gene therapy will not be efficacious (page 1782, col. 2, parag. 1, lines 1-4).

In view of the unpredictability and lack of success in the art at the time of filing, gene therapy can only be considered predictable in being shown not to work. Thus to overcome these teachings in the art the specification would need to supply direct, correlative guidance as to the vector, the promoter, the expression level, the route of delivery and dosage amounts/frequency that are effective in alleviating symptoms of disease using the claimed expression system. Thus, the need for working examples in appropriate animal model studies is critical. However, no such studies have been provided with respect to systemic in vivo delivery or administration of autologous hepatocytes obtained from a liver biopsy as suggested on p. 15. Further, there are no teachings in the specification that would provide the artisan with any treatment regime to achieve a therapeutic benefit by in vivo or ex vivo gene therapy. The specification does not address promoters or other expression regulatory sequences such as enhancers, introns, 3' untranslated sequences, that could be use in an expression vector to achieve therapeutic transgene levels. In addition, there is no correlation between vectors, cells comprising vectors, routes of delivery (e.g. direct, im, iv) or dosage amounts/frequencies for treating any of the liver diseases recited in the instant specification. Without such guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

When read in light of the instant specification, the claimed method for therapeutic gene delivery falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of

general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

Applicant's arguments filed 6/17/98 with respect to the prior cancelled claims 21-26 have been fully considered but they are not persuasive. The declaration of Dr. Barsoum has no probative value inasmuch as it describes results from in vivo gene transfer experiments in human colon and breast cancer models that were not described in the instant specification. The specification only discloses baculoviral-mediated gene transfer for liver diseases; thus, when read in light of the specification, the subject matter of the instant invention provides no nexus with the material described by Dr. Barsoum.

There is nothing to indicate that the record as a whole indicates that the initially-filed disclosure is sufficient to enable one of ordinary skill in the art to make and use the invention in accordance with the teachings of the specification, particularly in view of the lack of guidance or working examples for treating liver diseases. Not only do the cancer models presented in the declaration lack probative value in overcoming the prima facie case against enablement, but they appear to lack any real-world context of use, since none of the description described therein approximate in any way any real world therapeutic application. The working examples described therein did not involve systemic administration of vectors (especially not to liver), but they also

fail to provide any nexus to any real-world context of use for ex vivo gene therapy. Further, the experiment involving administration of *cancer cells* expressing hIFNβ does not provide any nexus for treatment of normal cancer or liver disease.

With regard to the response addressing the statement in the previous Office Action referring to the Boyce et al. publication (Proc. Natl. Acad. Sci., 93:2348-2352, 1996), specifically:

> "Much more work will be necessary to evaluate the safety and efficacy of AcMNPV as a tool for human gene therapy".

Applicants contend that "there is no legal or scientific basis for concluding that, in view of this quotation, the specification could not be considered enabling as of its filing date" (p. 4). This is not persuasive, particularly in view of inventor Boyce's own statement 18 months after the effective filing date of "much more work [being] necessary to evaluate the...efficacy of AcMNPV as a tool for human gene therapy". Although such a statement can be considered prophetic and would not necessarily contravene the enablement requirement as set forth by Applicants in their response on p. 4, the evidence of record fails to support any declaration relying on teachings from the instant specification to overcome a rejection over enablement. The declaration concerning treatment of colon or breast cancer shares no nexus with the teachings of the specification. Consequently, Applicants have failed to overcome the prima facie case against enablement.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in its recitation of part b) since it is unclear what is meant by "maintaining said cell under conditions such that said exogenous gene is expressed" within the context of having "administer[ed] a baculovirus [comprising the exogenous gene] to a mammal comprising the cell". "[M]aintaining said cell" within the context of mammal does not appear to be subject to the artisan's control, therefore it is unclear what is meant by part b) in the context of the claim. Moreover, the claim is indefinite in its recitation of a method for *introducing into a cell* a baculoviral vector comprising an exogenous gene, "wherein the baculovirus is introduced by administering the baculovirus to a mammal comprising the cell" since it is unclear what constitutes the metes and bounds of said administration and its circular recitation of "cell"--first in the context of "introducing" then later in the context of administering the baculovirus to mammal *comprising the cell*. Specifically, it is unclear whether the claim reads on systemic administration of baculoviral vectors in vivo, ex vivo administration of cells comprising baculoviral expression vectors, or both.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,731,182. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the '182' patent makes obvious the claimed subject matter of instant claim 1, because the issued claim recites a method of expression in a mammalian cell using a baculoviral vector and the mammals of the instant claim comprise an obvious source of such cells for practicing the method recited in the issued claim.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER